Visual Evoked Responses during Neonatal Respiratory Disorders in Low Birth Weight Infants

L. J. GRAZIANI^[23], E. D. WEITZMAN, AND G. PINEDA

Saul R. Korey Department of Neurology and the Rose F. Kennedy Center for Research in Mental Retardation and Human Development,
Albert Einstein College of Medicine, Bronx, New York, USA

Extract

By using a standard electroencephalograph and a signal averager, the visual evoked response (VER) to paired and single light flashes was recorded from the midline occipital scalp regions in 24 low birth weight infants, 13 of whom were studied during periods of respiratory difficulty. Eleven of the latter died in the neonatal period. In seven infants, at the onset and during marked hypoxemia caused by prolonged apnea or airway obstruction, the following VER abnormalities occurred alone or in combination: marked decrease in amplitude of summed responses, absent summed response to first stimulus of the paired flash, and absent summed responses to both stimuli of the paired flash. In six infants, complete loss of VER's and a marked decrease in electroencephalogram (EEG) amplitude were associated with severe hypoxemia. In four of the six, VER's returned to normal following resuscitation, indicating that severe bioelectric abnormalities may be reversible as the blood gases return toward normal and before permanent brain damage occurs. Following repeated or severe and prolonged hypoxemia in these same six infants, isoelectric EEG's and absent evoked responses recorded terminally persisted for 30 min-8 hr prior to cessation of heart activity; during the terminal period, resuscitative efforts resulted in improved blood gas measurements in four of the six but without return of the VER. Abnormalities in VER's were not found in other infants with respiratory distress in whom recordings were obtained prior to the onset of severe hypoxemia or prolonged apneic episodes. Of 10 infants who had neuropathologic examination, intracranial hemorrhage was found in 9 and intracerebral hemorrhage was found in 6. Five of the latter infants had abnormal neonatal VER's. The exact range of blood gas values associated with abnormal VER's could not be determined in our study, although normal responses were noted at P_{O_2} values as low as 34, 37, and 38 mm Hg in three infants. Normal VER's obtained in the infants without respiratory disorders were not always associated with normal neurologic examination in later infancy.

Speculation

The management of low birth weight infants with respiratory disorders is limited by the lack of methods which reliably and quantitatively evaluate neonatal cerebral function. Evoked responses to light flashes recorded from scalp EEG in premature infants and summed by signal averagers permit objective measurement of brain electrical activity. In low birth weight infants with respiratory difficulties, abnormal

VER's suggest an injurious effect of hypoxemia on cerebral bioelectric function. Abnormal evoked responses are reversible if resuscitation and correction of hypoxemia are prompt and successful. Thus, recording summed visual evoked responses may be useful for detecting and measuring acute brain injury in low birth weight infants receiving intensive care.

Introduction

Cerebral function is not easily studied in the human newborn. Neonatal neurologic reflexes, except those to visual stimuli, depend mainly upon structures other than cerebrum, and clinically are difficult to measure reliably. By contrast, visual evoked responses recorded from scalp EEG have been used to study quantitatively the bioelectric function and maturation of cerebral visual pathways in the neonate [4, 8, 16]. When summated by signal averagers, a visual evoked response (VER) to light flashes is consistently present in normal term and most premature infants. In this report, summed VER's to single and to paired light flashes were studied in 24 low birth weight infants, 13 of whom had respiratory difficulties during the recording (Table I). The results in the two infant groups were compared to determine whether acute abnormalities of

cerebral bioelectric function, as measured by the VER, occur in association with hypoxemia.

Subjects and Methods

Visual evoked responses to paired and single light flashes were recorded from midline occipital scalp regions in 24 low birth weight newborn infants during 69 EEG recording sessions. Recording electrodes (Beckman AgCl) were applied, using electrode paste and adhesive collars at theinion, 2 cm above theinion, at the vertex, and midway between vertex and nasion. Reference electrodes were applied to both ears. Resistances of 5,000–15,000 ohms were usually obtained. Electrodes applied to both ears were connected to *grid 1* and the scalp electrodes were connected to *grid 2* of a Grass model 6 electroencephalograph. The signals from the EEG amplifiers were summed algebraically on line, using a computer of average transients [17]. Prior to each recording session, a defined unidirectional square wave signal (20 μ v) was processed in the same way as the EEG signal and was used to calibrate the recording system. A photic stimulator, Grass model Ps2, set at maximal intensity, was placed 15–25 cm from the infant's face. Single or paired flash stimuli were delivered every 4 sec. Evoked responses to 50 or 100 consecutive single flashes were summed alternately with responses to 50 or 100 consecutive paired flashes of a constant defined interstimulus interval. The interstimulus intervals of the paired stimuli were 25, 50, 100, 150, 200, 250, and 350, or 500 msec. In the 11 stable infants at each EEG session of 4–6 hr, two to four summed VER's were recorded at each interstimulus interval (Table II) and written out on graph paper using an x-y plotter. The VER's to paired flashes from all subjects were inspected for R_1 , which is the summed response to the first stimulus of the pairs, and for R_2 , the summed response to the second stimulus. The R_2 was identified by noting waves of the appropriate latency and polarity which were not present in the summed response to single flashes (Fig. 1).

Thirteen infants were studied during periods of moderate to severe respiratory disorder including respiratory distress, apneic episodes, or airway obstruction.

Table I. Birth weight groups of 24 study infants

	540– 1050 g	1060– 1500 g	1510– 2200 g
VER ¹ during respiratory disorder, no.	6	4	3
VER in terminal period, no.	4	1	1
Deaths, no.	6	2	3
VER in stable infants, no.	4	4	3
Total studied, no.	10	8	6

¹ Summed visual evoked responses to single and paired light flashes.

Table II. Summed evoked responses to paired flashes in stable low birth weight infants¹

	Total trials ²	Present	%
Response (R_1) to stimulus (S_1)	464	458	98.7
Response (R_2) to stimulus (S_2)			
≤ 50 -msec interval	114	20	17.5
100-msec interval	112	65	58.0
150-msec interval	95	63	66.3
≥ 200 -msec interval	143	138	96.5

¹ Summed visual evoked responses to 50 or 100 paired flashes during 41 EEG sessions in 11 low birth weight infants without respiratory difficulties at time of recording.

² Number of summed responses.

tion, or combinations of the three. Respiratory distress was defined as a respiratory rate exceeding 65/min on two or more occasions, grunting respirations lasting more than 1 hr, or generalized cyanosis when breathing room air. The 11 stable infants had no respiratory distress at the time of the recording, although there was a history of severe birth asphyxia in 4 of them. In addition, recordings were obtained in the terminal period 30 min–8 hr preceding death in six infants with respiratory disorders. Complete autopsies were obtained in 10 infants, and in 1 infant the lungs but not the brain were examined. Surviving infants were studied every 2–3 weeks, using the same stimulus and recording conditions until discharged from the nursery. Blood samples in 4 stable infants and 13 infants with respiratory disorders were obtained from the umbilical artery or from warmed heel puncture at least once during the recording session. In addition, blood gas measurements were obtained in 7 of the 13 infants following the onset of each recognized episode of airway difficulty or acute cyanosis. The summed VER's recorded following the onset of each episode and within 14 min of the blood sample were compared with previous VER's in the same infant and with those recorded in the stable infants. Visual evoked responses were either not recorded during resuscitation or were not scored because of movement artifact. Following each resuscitation, another blood gas sample was obtained and the two summed VER's recorded within the subsequent 14-min period were evaluated. In six infants, blood gas measurements were obtained at least twice during the recording of an irreversible isoelectric EEG and absent VER's prior to death (Table III). P_{O_2} , P_{CO_2} , and pH were measured in an Instrument Laboratory blood gas analyzer. All 24 infants studied were less than 38-week gestation. Four infants who died were 2 sd below mean weight for gestational age. The other 20 infants were of appropriate weight for gestation, which ranged from 28 to 35 weeks.

Results

A prominent summed VER to single flashes was recorded over the occipital area in all infants, and was similar in wave form and latency to that reported by others [5, 11, 16]. Infants without respiratory difficulty and less than 36 weeks postconception at the time of recording had VER's which were characterized by a prominent negative wave with a peak latency of 250–350 msec at the occipital area, frequently followed by a smaller positive and negative wave and an incon-

Fig. 1. Averaged evoked responses to 100 single and 100 paired light flashes during sleep in low birth weight infant, postnatal age 1 week (birth weight, 1060 g; gestational age, 28 weeks). No neonatal respiratory difficulties were noted and blood gas measurements were normal prior to study. The interval between the first (S_1) and the second (S_2) of the flash pair is indicated for each averaged response. R_1 and R_2 are the first and second response to S_1 and S_2 , respectively. Flash, single or pair, delivered every 4 sec. Total analysis time 1 sec; active electrode, Oz, at inion. Reference, A, both ears. Positive deflection at Oz is upward.

stant late positive wave at 450–650 msec (Fig. 1). A small positive wave preceding the first negative wave was not seen before 33-weeks postconception and was not constant until after 36 weeks.

Four hundred sixty-four summed VER's to paired flashes during 41 recording sessions were analyzed in 11 low birth weight infants without respiratory difficulty at the time of the recording (Table II). A response to the second flash of the pair (R_2) was present at interstimulus intervals of 200 msec or more in all 11 infants, in all recording sessions, and for most of the trials. An R_2 was never present at interstimulus intervals of 25 msec. At interstimulus intervals of 50 msec, an R_2 was present in 20 of the trials of seven infants and absent in four infants; this probably could not be attributed to maturation, since two of the latter infants were below 32 and two were above 34-week post-

Table III. Infants with summed VER's¹ during respiratory distress

Sub- ject	Birth wt, g	Gesta- tion, weeks	VER, paired flashes ²						PO ₂ arterial or capillary ³			Pulmonary pathology		Brain pathology
			A	B	C	D	E	F	N VER	R VER	Ab I VER			
1	800	26	+	+	+	+	+		48-210	17-36	36-100	Hyaline membrane hemorrhage	disease;	Subependymal, subarachnoid, and intraventricular hemorrhage
2	890	28	+	+	+	+	+		*54-210	11-44	17-56	Hyaline membrane disease		Not examined
3	960	28	+	+	+	+	+		37-200	8-40	56-70	Hyaline membrane hemorrhage	disease;	Subependymal, subarachnoid and intraventricular hemorrhage
4	1050	30	-	+	+	+	+		34-160	22-37	8-88	Atelectasis		Kernicterus; subependymal hemorrhage
5	1390	31	+	+	-	+	-		*64-144	16		Survived		Survived
6	1480	32			+	-	+				9-47	Hyaline membrane atelectasis	disease;	Subependymal hemorrhage
7	1750	34	+	+	+	-	+		38-45		17-25	Hyaline membrane hemorrhage	disease;	Subarachnoid and subependymal hemorrhage
8	540	26						+	*84			Atelectasis; emphysema		Subependymal and intraventricular hemorrhage
9	690	26						+	*50-72			Atelectasis; emphysema		Subarachnoid hemorrhage
10	1200	29						+	54-290			Survived		Survived
11	1480	30						+	*128			Hyaline membrane hemorrhage	disease;	Subarachnoid and subdural hematoma; periventricular congestion
12	1510	36						+	58-60			Hyaline membrane disease		Subarachnoid hemorrhage; periventricular leucomalacia
13	1560	30						+	47-77			Hyaline membrane disease		Periventricular capillary congestion

¹ VER: visual evoked response.² Summed visual evoked responses to paired light flashes. A: R₁ absent but R₂ present at 200-msec or greater interval during hypoxemia. B: Decreased amplitude of responses during hypoxemia. C: Absent R₁ and R₂ during hypoxemia. D: Abnormalities reversed following resuscitation. E: Recordings obtained at the time of death (isoelectric EEG and absent response). F: No abnormal VER's during recording.³ Partial pressure O₂ (mm Hg) in umbilical artery or in capillary blood. Asterisk (*) indicates blood from warmed heel puncture. N VER: PO₂ range during normal visual evoked response. R VER Ab: PO₂ range during reversible visual evoked response abnormalities. I VER Ab: PO₂ range during irreversible visual evoked response abnormalities.

conception age. The R₂ was frequently of slightly greater amplitude than R₁ (Fig. 1). Of the 13 low birth weight infants studied during periods of respiratory distress, apneic episodes, or airway obstruction, 11 died in the neonatal period (Table I). Since all infants with respiratory difficulties were 35 weeks or less postconception when initially studied, the prominent negative wave 250-350 msec following the stimulus was identified as R₁ or R₂. When compared with results from the stable infants, the following VER abnormalities occurred alone or in combination in seven infants at the onset and during severe respiratory difficulty: absent R₁, absent R₁ and R₂, and a marked decrease in R₁ and R₂ amplitude (Table III). A decrease in amplitude of the summed R₁ or R₂ to one-third or less that of the immediately preceding VER was considered significant inasmuch as an acute decrease of that magnitude was not noted in any of the stable infants less than 35 weeks postconception. Abnormalities in evoked responses were not noted in any of the seven infants until marked hypoxemia caused by prolonged apnea or airway obstruction occurred; all seven were treated at some time during their nursery course with endotracheal intubation and mechanical ventilation.

When severe hypoxia persisted, complete loss of VER's and an isoelectric EEG or a marked decrease in EEG amplitude were observed in six infants; in four of them, VER's returned to normal following resuscitation. These severe bioelectric abnormalities are therefore reversible if blood gases return toward normal before severe brain dysfunction occurs (Figs. 2 and 3). After repeated or severe and prolonged hypoxemia, an isoelectric EEG and absent VER's were recorded for 30 min and up to 8 hr prior to cessation of heart activity in six infants; resuscitative efforts resulted in the return of blood gases toward normal in four of the six infants during the terminal period of absent EEG activity (Table III). In two infants (subjects 1 and 2, Table III), during three prolonged apneic episodes with cyanosis, the amplitude of summed VER's to single flashes decreased markedly without more than a 50-msec increase in latency. (Blood gas measurements were not obtained during these apneic episodes because of the initiation of resuscitative efforts.) Abnormalities in VER's or EEG were not found in six other infants with less severe respiratory distress in whom recordings were obtained early in their neonatal course. Arterial blood gases which were obtained dur-

Fig. 2. Averaged evoked responses to single and paired (150 msec interval) light flashes in low birth weight infant, postnatal age 46 hr, with respiratory distress on Bird respirator and endotracheal tube (subject 1, Table III). S₁ and S₂ are the first and second of the flash pair, respectively; R₁ and R₂, first and second response to S₁ and S₂, respectively. A: response to single flash. B: response to paired flash. C: recorded during onset of hypoxemic episode apparently caused by obstruction of endotracheal tube; R₁ and R₂ amplitude both decreased. D: recorded immediately following C, cyanosis noted during recording; R₁ and R₂ almost absent. E: recorded following reintubation, positive pressure O₂ and intravenous bicarbonate; R₂ amplitude less than R₁. F: recorded 800 sec after E; R₂ amplitude greater than R₁ and response similar to B. Blood gases measured at completion of recordings B, D, and F. Positive deflection at active electrode, Oz, is upward.

Fig. 3. Averaged evoked responses to paired light flashes in low birth weight infant with respiratory distress (subject 3, Table III). Endotracheal tube and Bird respirator initiated at age 8 hr and continued because of prolonged apneic episodes. S₁ and S₂ are the first and second of the flash pair, respectively; R₁ and R₂, first and second response to S₁ and S₂, respectively. Paired flash interval, 200 msec except in trace D. A: response to 100 paired flashes. B: averaged response recorded during 400 sec following recording A; slight cyanosis noted, R₁ is absent. C: averaged response recorded during 400 sec following B; marked cyanosis noted, R₁ and R₂ are absent. D: recorded following 7 min of resuscitation; return of evoked responses to paired flash of 150 msec interval. E: averaged evoked response following approximately 11 min of hypoxia during which P_{O₂} was below 10 mm Hg; absent responses persist despite improved blood gases. Blood gases measured at completion of C, D, and E. Positive deflection at active electrode, Oz, is upward.

ing EEG recording in this group disclosed P_{O_2} values ranging from 47 to 290 mm Hg (Table III); after the EEG and evoked response recordings were discontinued, the clinical condition of five of these six infants worsened and death followed severe hypoxemia or prolonged apnea, or both.

Of 10 infants who had neuropathologic examination, intracranial hemorrhage was found in 9 and intracerebral hemorrhage in 6. Five of the latter infants had abnormal neonatal VER's. Thrombosis of the portal and umbilical veins was also noted in two, and focal necrosis of the liver in one other infant given fluids via an umbilical vein. Arterial thrombosis was not found in any of the infants given fluids via an umbilical artery catheter or in whom blood samples were obtained from the umbilical artery.

One of the infants with abnormal summed VER's during two separate periods of apnea survived (*subject 5*, Table III). When last examined at age 27 months, the child's neurologic and developmental examination was normal, although he displayed hyperactive behavior. Normal VER's obtained in those neonatal infants without respiratory difficulties were not necessarily associated with normal neurologic examination in later infancy. Follow-up examinations were obtained in five infants after 1 year of age, and three were neurologically normal. In one of the two children with developmental retardation, prolonged apnea occurred at birth, yet normal VER's were recorded at age 30 hr and at 2-week intervals for six sessions. The other infant with normal neonatal VER's and EEG's who is known to have developmental retardation did not have a history of asphyxia at birth or complications in the neonatal period.

The acute changes noted in the amplitude of the summed VER during episodes of hypoxemia and following resuscitation in a low birth weight infant are illustrated in Figure 2 (*subject 1*, Table III). Recording was begun at age 29 hr. Following each of four separate episodes of severe hypoxemia associated with loss of evoked responses, successful resuscitation was accomplished, with immediate return of VER's. An isoelectric tracing with absent summed VER's followed the fifth hypoxemia episode, and cardiac action ceased 3.5 hr later. Figure 3 (*subject 3*, Table III) illustrates the loss of R_1 but not R_2 at the onset of hypoxemia, followed by the loss of both responses. Cardiac action ceased after 8 hr of isoelectric EEG tracing and absent VER's.

The ink-writer EEG's were not completely analyzed for amplitude or frequency, but intervals recorded

during abnormal responses were reviewed. In general, a marked decrease in EEG amplitude usually occurred during each period of severe hypoxemia associated with abnormal or absent VER.

Discussion

Although hypoxemia and, to a lesser extent, hypercapnia and acidosis may be injurious to nerve tissue, a causal relation between neonatal respiratory disorders and brain injury is uncertain. In an autopsy study of premature infants, respiratory difficulties, especially apnea, during the neonatal period were associated with intracranial hemorrhage and damage to the highly active and cellular periventricular area [2, 15]; yet in a follow-up study of low birth weight infants, there was no unexpected increased incidence of neurologic sequelae among the survivors of neonatal respiratory distress [1]. Primary brain hemorrhage, rather than an effect of hypoxia, may be the cause of respiratory difficulty and apneic episodes [12]. Electroencephalogram recordings during neonatal respiratory difficulties may therefore be helpful in evaluating possible injurious effects of hypoxemia on cerebral bioelectric activity. Hypoxemia resulting in cerebral hypoxia alters EEG activity in animals and in adult man [9], but little similar information about human newborns is available. In a study of low birth weight infants with severe neonatal respiratory disease, EEG amplitude decreased significantly when P_{O_2} measurements in umbilical arterial blood decreased to below 40 mm Hg or when a rapid fall from high normal values to approximately 40 mm Hg occurred [14]. Virtually no EEG activity was present during the first 24 hr of life in infants less than 25-week gestation and in infants between 28- and 34-week gestation who had experienced birth asphyxia, yet inactive EEG's were not necessarily incompatible with survival and apparently normal development. Also, in another report [3], prolonged periods of markedly low voltage EEG activity were described in otherwise normal premature infants of 36 weeks or less postconception. Thus, in young premature infants, the routine EEG is limited by the difficulty in defining abnormal tracings.

Visual evoked response studies in the neonatal period have been of value in evaluating the maturation of brain electrical activity [5, 8], yet the clinical usefulness of recording VER's in the neonatal period is at present uncertain. Visual evoked response abnormalities, not well described, have been reported in neonatal infants with suspected perinatal brain damage [10];

but, because intra- and intersubject variability in characteristics of summed VER's recorded from normal infants has not been satisfactorily explained, changes must be marked or the response must be absent before being considered abnormal [6]. Also, abnormal responses are in general nonspecific and their prognostic significance unknown, whereas normal responses do not necessarily imply functional or structural integrity of visual pathways [7]. In this report, recordings were analyzed for the presence or absence of the summed response and for marked depression of amplitude to avoid the difficulty in interpretation of more variable wave form characteristics. Absent summed VER's to both single and paired flashes were noted only in infants with respiratory disorders. In the stable infants, 96.5% of summed VER's to paired flashes of 200-msec or greater interstimulus interval disclosed both an R_1 and R_2 ; an absent R_1 was observed in only 1.3% of the summed VER's regardless of the interstimulus interval of the paired stimuli (Table II). Thus, absence of summed VER's to single flashes or to either of the paired flashes of 200-msec or more interstimulus interval was a relatively certain abnormality and easily recognized by visual inspection of the recordings.

An evoked response to the second stimulus of the paired flashes presumably depends upon rapid repolarization of neurons within the visual system, and theoretically may be a more sensitive indicator of abnormal brain metabolism than responses to a single flash. Therefore, absence or marked depression of a summed R_1 in the presence of a summed R_2 , as found in five of the infants during severe respiratory difficulties (Table III), was unexpected and is not easily explained. Possibly, temporal recruitment occurred during hypoxemia or, alternatively, latency of R_1 increased and R_2 was indeed absent. However, the amplitudes of summed responses to single flashes were also markedly diminished during episodes of presumed hypoxemia in two infants while latencies changed less than 100 msec. Also, in those summed VER's with a labeled R_2 only, the latency of the wave was always that expected for the interstimulus interval of the flash pair when compared with normal VER's in the same infant (Fig. 3). This explanation for the single response to paired stimuli, however, could be proved only by determining the latencies of summed responses to single and paired flashes delivered alternately during the same recording period. The abnormalities in VER's are probably not due to effects on the retina, which is more resistant to hypoxemia than the cerebrum [13]. Since normal VER's recorded during the neonatal course were asso-

ciated with abnormal development at follow-up in two of the five infants examined after age 1 year, prenatal or perinatal brain injury may have occurred without simultaneous or subsequent change in VER's. Alternatively, the developmental abnormalities may have been the result of injurious agents and environmental factors in the postneonatal period.

The exact range of blood gas values associated with abnormal VER's could not be determined in our study. Blood pressure was not monitored and, when severe hypoxemia occurred, P_{CO_2} and blood pH were usually also markedly abnormal. P_{CO_2} , blood pressure, and, to a lesser extent, blood pH, by their influence on cerebral blood flow, may alter the effects of hypoxemia on brain. Also, previous cerebral damage from any cause may irreversibly change EEG activity regardless of subsequent resuscitation and blood gas measurements (Fig. 3 and Table III). Therefore, a correlation between P_{O_2} values alone and EEG measurements are difficult to establish. Nevertheless, the limits of hypoxemia beyond which VER's became abnormal were determined in seven infants, and absent VER's with an isoelectric EEG following resuscitative efforts were indications of irreversible brain damage incompatible with survival in six infants age 6 hr to 3 days. The present study therefore describes a method for measuring objectively the bioelectric reactivity in infants with neonatal respiratory disorders. In an individual infant, the absence of summed responses to single or paired flashes during or following severe respiratory difficulty suggests an adverse effect of hypoxemia on brain electrical activity. Further studies are necessary to determine the long range prognostic significance of VER abnormalities in the neonatal period.

Summary

Summed visual evoked responses to paired light flashes were recorded from the midline occipital scalp region in 24 low birth weight infants during the neonatal period. Thirteen infants were studied during acute respiratory difficulties, and abnormalities in VER's were noted in seven of them. In some, VER's returned to normal following resuscitation, indicating that severe EEG abnormalities may be reversible if severe hypoxemia is corrected before permanent brain damage occurs. Significant intracerebral hemorrhages were present at autopsy in all infants who had abnormal evoked responses and who had neuropathologic examinations. Normal VER's obtained in infants without respiratory disorders were not of reliable predic-

tive value since they were not necessarily associated with normal neurologic examination in later infancy. The results of the study suggest that, in an individual low birth weight infant with respiratory difficulty, the acute harmful effect of severe hypoxemia on brain electrical activity may be disclosed by recording summed responses to single and paired flashes.

References and Notes

1. AMBRUS, C. M., WEINTRAUB, D. H., NISWANDER, K. R., FISCHER, L., FLEISHMAN, J., BROSS, I. D., AND AMBRUS, J. L.: Evaluation of survivors of respiratory distress syndrome at 4 years of age. *Amer. J. Dis. Child.*, **120**: 296 (1970).
2. BANKER, B. Q.: The neuropathological effects of anoxia and hypoglycemia in the newborn. *Develop. Med. Child Neurol.*, **9**: 544 (1967).
3. DREYFUS-BRISAC, C., CUKIER, F., AND MOREL-KAHN, F.: Le trace paroxystique: Sa valeur pronostique suivant le degre de prematurite. *Revue Neuropsychiat. Infantile*, **17**: 795 (1969).
4. ELLINGSON, R. J.: Cerebral electrical responses to auditory visual stimuli in the infant (human and subhuman studies). In: P. Kellaway and I. Peterson: *Neurological and Electroencephalographic Correlative Studies in Infancy*, p. 78. (Grune and Stratton, New York, 1964).
5. ELLINGSON, R. J.: The study of brain electrical activity in infants. In: L. P. Lipsitt and C. C. Spiker: *Advances in Child Development and Behavior*, Vol. 3, p. 53. (Academic Press, New York, 1967).
6. ELLINGSON, R. J.: Variability of visual evoked responses in the human newborn. *Electroencephalogr. Clin. Neurophysiol.*, **27**: 10 (1970).
7. ELLINGSON, R. J., AND SCHAIN, R. J.: EEG patterns in juvenile cerebral lipidosis. *Electroencephalogr. Clin. Neurophysiol.*, **27**: 191 (1969).
8. ENGEL, R., AND BENSON, R. C.: Estimate of conceptional age by evoked response activity. *Biol. Neonatorum*, **12**: 201 (1968).
9. GASTAUT, H., RISCHGOLD, H., AND MEYER, J. S.: Conclusions of the international colloquium on anoxia and the EEG. In: H. Gastaut and J. S. Meyer: *Cerebral Anoxia and the Electroencephalogram*, p. 599. (Charles C Thomas, Springfield, Ill., 1967).
10. HRBEK, A., AND MARES, P.: Cortical evoked responses to visual stimulation in full-term and premature newborns. *Electroencephalogr. Clin. Neurophysiol.*, **16**: 575 (1964).
11. LODGE, A., ARMINGTON, J. C., BARNET, A. B., SHANKS, B. L., AND NEWCOMB, C. N.: Newborn infants' electroretinograms and evoked electroencephalographic responses to orange and white light. *Child Develop.*, **40**: 267 (1969).
12. MINKOWSKI, A.: The neuro-respiratory distress syndrome. *Proc. Roy. Soc. Med.*, **58**: 1 (1965).
13. NOELL, W., AND BUFFALO, M.: Differentiation, metabolic organization and viability of the visual cell. *Arch. Ophthalmol.*, **60**: 702 (1958).
14. ROBERTSON, N. R. C.: Effect of acute hypoxia on blood pressure and electroencephalogram of newborn babies. *Arch. Dis. Childhood*, **44**: 719 (1969).
15. TOWBIN, A.: Cerebral hypoxic damage in fetus and newborn. *Arch. Neurol.*, **20**: 35 (1969).
16. UMEZAKI, H., AND MORRELL, F.: Developmental study of photic evoked responses in premature infants. *Electroencephalogr., Clin. Neurophysiol.*, **28**: 55 (1970).
17. CAT 400A, Mnemotron Corporation.
18. Informed consent was obtained from parents of all infants in this study.
19. Presented in part at the Society for Pediatric Research, Atlantic City, N. J., May, 1969.
20. The authors wish to thank Drs. Harry H. Gordon, Dominic Purpura, and Robert Terry for their invaluable support and suggestions, and to acknowledge with gratitude the help of Edward Costigan, Myra Pinkowitz, Enid Bellamy, Winifred Minott, and the nursing staff of the premature nursery, Bronx Municipal Hospital Center.
21. Supported by Grants HD-01405, NB-05325, NB-5114, NB-03356, NB-04174, 5 T01 NS05135-14, and by a grant from the Edward Noble Foundation. During the study, Drs. L. Graziani and E. Weitzman were Career Scientists, Health Research Council of the City of New York.
22. Dr. L. J. Graziani's present address is: Departments of Neurology and Pediatrics, Thomas Jefferson University, Philadelphia, Penna. Dr. E. Weitzman's present address is: Department of Neurology, Montefiore Hospital and Medical Center, Bronx, N. Y.
23. Requests for reprints should be addressed to: L. J. GRAZIANI, M.D., Department of Neurology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Penna. 19107 (USA).
24. Accepted for publication August 31, 1971.